

The Etiology of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is the most common dementia disorder; its global prevalence has increased during recent years. The disease is characterized by oxidative stress, mitochondrial impairment, neuro-inflammation, synaptic dysfunction, and blood-brain barrier disruption, which may be caused in part by abnormal extracellular accumulation of amyloid- β peptide (**A β**) in amyloid plaques and tau protein aggregation in intracellular neuro fibrillary tangles (**NFTs**), which are the hallmarks of Alzheimer's disease, causing synaptic and neuronal loss and enhancing cognitive dysfunction. Epidemiological, clinical and experimental data support the following hypotheses of AD pathogenesis, described in this chapter: the amyloid, the tau, the cholinergic, the mitochondrial, the metabolic and the vascular. It is important that further research be conducted with regard to each one of them; in order to obtain new evidence and new proposals for the treatment of AD may be generated.

INTRODUCTION

Neuro degeneration is a progressive functional or structural neuronal loss related to various etiologies such as genetic mutation (less than 5%), incorrect protein folding and deficiency in the degradation pathways, damage in membrane neurons, mitochondrial dysfunction, oxidative stress, toxic molecule formation, and neuro-inflammatory processes. Neuro degeneration has been associated with diseases such as Alzheimer's, Parkinson's, Huntington's, Amyotrophic Lateral Sclerosis, among others [1,2].

Alzheimer's Disease (**AD**) is the most common cause of neuro degeneration and the consequent intellectual decline in the elderly population worldwide, with a prevalence of 44 million people, mostly over 60 years of age, throughout the world in 2015 and this figure is estimated to have doubled by 2050 [3]. AD is characterized by memory impairment, deficit in other cognitive domains as well as non-cognitive neurological deficits. It is the most common form of dementia. Dementia is a syndromic term to describe the loss of previously acquired cognitive abilities; neurodegenerative diseases represent the most common causes of dementia.

Among individuals over 65 years of age, approximately 6% have AD and among those over 85 years of age, the prevalence of the disease is close to 30%. It is therefore a disease that produces a very significant social impact, leading to considerable impairment in quality of life for patients, family members, and healthcare workers. Among the earliest symptoms of AD are memory loss and language problems.

Diagnosis of AD or related NCDs is based on the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders (**DSM-V**) [4] from the American Psychiatric Association and the International Classification of Diseases (**ICD 10**) of the World Health Organization. Additionally, in the absence of good biomarkers, diagnosis of AD is made based on inclusion and exclusion criteria of the National Institute of Neurological and Communicative Disorders and Stroke (**NINCDS**) and the Alzheimer's disease and Related Disorders Association (**ADRDA**), the DSM-V and ICD-10 [5]. The NINCDS/ADRDA criteria include support elements and establish the diagnosis of AD as possible, probable, or definite; these criteria are summarized in Table 1. AD can be diagnosed with 90% confidence based on clinical criteria such as medical history, laboratory tests, neuro imaging, and neuropsychological evaluation [6,7].

Table 1: NINCDS/ADRA Criteria.

AD criteria possible
* Dementia with variations in their onset, or clinical course, unusual in AD, without alternative explanation.
* In the presence of a second systemic or brain secondary disorder capable of producing dementia.
* When there is a gradual and progressive deficit of cognitive functions.
AD criteria probable
* Cognitive deficit demonstrated by clinical examination.
* Deficits in two or more cognitive areas such as memory, judgment or calculation.
* Progressive deterioration of memory and other cognitive functions.
* Absence of disorders of consciousness such as delirium.
* Onset between 40 and 90 years old.
* No-evidence of other systemic or brain diseases that can demonstrate the clinical picture.
* Presence of aphasia, apraxia or agnosia.
* Inability to perform daily activities.
* Family history of AD.
* Complementary tests: X-ray computed tomography and computerized axial tomography scan, etc
AD criteria definite
* <i>Post-mortem</i> histo pathologic confirmation.

Although these criteria exist so that a more accurate diagnosis may be made, the NINCDS and the ADRDA have searched for new biomarkers able to diagnose the disease with 100% confidence before the patient dies.

PATHOLOGY

The disease is characterized by oxidative stress, mitochondrial impairment, neuroinflammation, synaptic dysfunction, and blood-brain barrier disruption, which may be caused in part by abnormal extracellular accumulation of amyloid- β peptide (**A β**) in amyloid plaques and tau protein aggregation in intracellular neuro fibrillary tangles (**NFTs**), which are the hallmarks of Alzheimer's disease, causing synaptic and neuronal loss and enhancing cognitive dysfunction.

AD can be classified into two types according to the age of onset and pathological factors. The first type, early-onset AD (**EOAD**) or familial AD (<60 years of age) occurs in 5% of all cases of AD in individuals with a family history of at least three generations [3]. Approximately 50% of EOAD cases carry mutations in one of the presenilin-1 (**PSEN-1**), presenilin-2 (**PSEN-2**) or amyloid precursor protein (**APP**) genes [8]. The identification of mutations in these genes has not only provided important insights into the molecular mechanisms and pathways involved in the pathogenesis of AD, but it has also led to valuable targets currently used in diagnosis and drug development. In these patients more than 230 mutations have been identified in one of the three genes involved in EOAD. These mutations increase the production of the 42-amino acid form of amyloid- β (**A β 42**), the most common neurotoxic fragment in AD patients, resulting in a younger age of EOAD onset [9]. The other type of Alzheimer's disease is late-onset AD (**LOAD**)

or sporadic AD (>65 years of age), which usually has a sporadic occurrence and is multifactorial, hence its name. Risk factors that occur with greater incidence in patients with LOAD are diabetes, hypertension, hypercholesterolemia, obesity, and metabolic syndrome, which are related to lipid metabolism. LOAD has been linked to oxidative stress phenomena, mitochondrial damage, and ApoE polymorphism in the vascular endothelium [10], which involves an increase in A β ₄₂ fragment levels, leading to an elevation in amyloid plaque formation and excitotoxic processes.

CURRENT ETIOLOGICAL HYPOTHESIS OF AD

The neuropathological features of both forms of AD are characterized by abnormal extracellular accumulation of amyloid- β peptide (**A β**) in amyloid plaques and tau protein aggregation in intracellular neurofibrillary tangles (**NFTs**) [11]. Epidemiological, clinical and experimental data support several hypothesis of AD pathogenesis.

The Amyloid Hypothesis

The main hypothesis of AD pathogenesis is the amyloid cascade hypothesis, positioning amyloid aggregation as the mechanistic initiation event, where different stages of abnormal aggregates, from soluble oligomers to insoluble fibers or plaques, cause impaired synaptic function and neuronal damage, leading to chronic neurodegeneration characterized by cognitive impairment and ultimately dementia [12]. Related to this hypothesis, the accumulation of A β plaques acts as an enhancer in the pathological cascade, including neurite damage and neurofibrillary tangle (**NFT**) formation via tau protein, leading to neuronal dysfunction and cell death in AD. Genetic, biochemical, and pathological evidence support the amyloid cascade hypothesis, which postulates that the accumulation and aggregation of A β plaques is the main cause of AD [13]. It has been proposed that neurotoxic accumulation of A β in the brain results from an imbalance in A β -peptide homeostasis [14].

A β plaques consist of a principal protein component called A β peptide. A β peptides are formed by 39-43 amino acid residues derived proteolytically from the sequential enzymatic action of β -secretase and γ -secretase complex in the amyloid precursor protein (**APP**) [12], which is widely distributed in the neuron membrane [15]. A β -peptide length varies in the C-terminal according to the pattern of APP cleavage. The A β ₁₋₄₀ isoform is the most prevalent peptide, followed by A β ₁₋₄₂ peptide, which is hydrophobic in nature and generates aggregates at a much faster rate than A β ₁₋₄₀ [16]. Also, within plaques, A β -peptides have a β -sheet conformation and polymerize in structurally different forms including fibrillar oligomers, protofibrillar structures and polymorphic oligomers [17]. A β deposition and diffuse plaque formation lead to local processes such as microglial activation, cytokine release, reactive astrocytosis, and inflammatory response of multiple proteins. There are several physiological mechanisms of clearance that prevent amyloid aggregation and deposition and aid in the removal of A β from the brain; among these processes are transvascular clearance across the blood-brain barrier (**BBB**), the constant flow of interstitial fluid, cerebrospinal fluid (**CSF**) absorption, and enzymatic degradation [18]. If A β -

peptide is not removed from the brain, it can cause multiple biochemical and structural changes around the axons, dendrites, and cell bodies of neurons characterized by the loss of synapses, the loss or decrease in the number of neurons, and brain atrophy in AD patients [13].

The Tau Hypothesis

Tau proteins are found mainly in neurons and belong to the family of microtubule-associated protein (**MAP**); they develop long processes such as axons and dendrites for neuronal transmission. In the adult brain six tau protein isoforms derived by alternative splicing of gene have been identified; they are located on the long arm of chromosome 17. These proteins play an important role in microtubule assembly and neuronal microtubule network stabilization [11]. The most striking feature of tau protein is the presence of a microtubule binding domain consisting of three to four highly-conserved 18 amino acids repeats located at the C-terminal in the middle protein. This microtubule binding domain is involved in polymerization and microtubule stabilization [13].

Tau protein deposition in insoluble aggregates results in a loss of tau function, leading to microtubule instability and promoting neurodegeneration. Intact microtubules are required for axonal transport and normal neuronal function; it has long been recognized that microtubule destabilization causes AD [19]. Tau phosphorylation is regulated from fetal development to adulthood. Tau protein in the immature brain is phosphorylated at six to eight sites on the shorter isoforms, whereas in the adult brain, two to three phosphorylation sites are present in six isoforms. The microtubule-binding capacity of tau protein can effectively regulate post-translationally by modulating phosphorylation of serine or threonine [13]. The tau microtubule-binding domain (**MBD**) has four repeat sequences (**R1-R4**) of serine (**S**) and threonine (**T**), followed by proline (**P**). These amino acids are hyper phosphorylated by glycogen synthase kinase 3 β (**GSK-3 β**), cyclin-dependent kinase 5 (**Cdk5**), and their p25 activator subunit or mitogen-activated protein kinase (**MAPK**). Similarly, kinases targeted at sites without proline such as Akt, Fyn, protein kinase A (**PKA**), calcium-calmodulin-dependent protein kinase 2 (**CaMKII**), and microtubule affinity-regulating kinase (**MARK**) also are involved in the hyper phosphorylation of tau protein [20].

In pathological conditions an abnormal increase in levels of hyperphosphorylated tau protein has been observed in the cytosol. Hyperphosphorylated tau proteins are polymerized in paired helical filaments and straight filaments referred to as tangles or NFTs [21]. The loss of normal tau function leads to pathological alterations in the structural and regulatory functions of the cytoskeleton; thus, the normal cellular functions of neurons such as maintenance of proper morphology, axonal transport, synaptic dysfunction, and neurodegeneration are affected [22].

The Cholinergic Hypothesis

For many years, the cholinergic hypothesis has been the center of study dementias and other neurodegenerative diseases. Acetylcholine is a neurotransmitter that is responsible for the

conduction of electrical impulses from one nerve cell to another. It is produced in the cell body from choline and acetyl coenzyme A and is transported through microtubules to the synaptic button, where it is released into the synaptic space and binds to two receptor types: nicotinic (ionotropic) receptors, which are fast, and muscarinic (metabotropic) receptors, which are slower; in individuals with neurodegeneration as in AD, levels of this neurotransmitter are decreased due to its rapid hydrolysis by acetyl cholinesterase (**AChE**) [23]. AChE belongs to the α/β -fold family of proteins, since it consists of stranded central β -sheets surrounded by α -helices [24]. It has been proposed that AChE produces non-cholinergic functions such as A β deposition and formation of NFTs in the brain of AD patients [25]. In fact, a specific cholinergic deficit, involving cholinergic projection from a basal forebrain neuronal population, the nucleus basalis of Meynert, to the cortex and hippocampus has been found in the brains of AD patients [26].

The Mitochondrial Cascade Hypothesis

The mitochondrial cascade hypothesis has been associated with mitochondrial DNA (**mtDNA**) mutations, oxidative stress, and the presence of A β in mitochondria, which plays an important part in AD pathogenesis, because this induces mitochondrial dysfunction and neuronal apoptosis [2]. The mtDNA mutations include CD2-associated protein, which induces mitochondrial fission and transport damage along axons due to dynamic actin remodeling [27]. Mitochondrial A β levels could be regulated by APP, which may be targeted to the outer mitochondrial membrane and interfere with protein import [28]. Mitochondrial A β levels induce electron transport chain complex I and IV inhibition and decrease ATP production.

A β interaction with the opening of the mitochondrial permeability transition pore induces an electrolyte imbalance across the inner mitochondrial membrane; this disruption between the mitochondria and cytosol allows the release of accumulated calcium. Inappropriate calcium levels in cells may contribute to neuronal stress by protease and phospholipase activation, particularly calpain and phospholipase A2 respectively. Calpain induces proteolysis, leading to degradation of cytoskeletal proteins and phospholipase A2 acts on membrane phospholipids and hydrolyzes mitochondria fragmentation; these processes enable the release of cytochrome C. In turn, cytochrome C activates the caspases pathway and initiates apoptosis [1,29]. However, the presence of A β in mitochondria can be inhibited by α -ketoglutarate dehydrogenase and alcohol dehydrogenase; these enzymes act as control points in the citric acid cycle, but their inhibition produces oxidative stress in the mitochondria. Mitochondrial oxidative stresses induce tau hyperphosphorylation, through the superoxide dismutase activity decrease associated with A β and glycogen synthase kinase 3 activation [28].

The Metabolic Hypothesis

The metabolic hypothesis holds that the disease is caused by changes in metabolic processes such as obesity, diabetes, hypercholesterolemia, and others. Recent research suggests that there are strong relationships between AD and type 2 diabetes mellitus (**T2DM**). T2DM and obesity

as well as a chronically high intake of fats, mainly of saturated fatty acids, have been linked to a deterioration of cognitive functions, which is a strong risk factor for dementia, including AD [30]. T2DM is another prevalent disease associated with obesity and often with aging; it is considered a risk factor for AD. T2DM is characterized by high levels of blood glucose resulting in production of increased hepatic glucose, impaired insulin production by β -pancreatic cells, and insulin resistance [31]. T2DM patients have a higher risk of cerebral complications, including stroke, cognitive impairment, and dementia, in addition to a set of systemic complications, such as retinopathy, nephropathy, and peripheral neuropathy, along with abnormalities in the microcirculation and macrovascular injuries in several systemic arteries [32].

The pathogenetic mechanisms through which T2DM causes cognitive impairment are not clearly established. The proposed scenarios connecting diabetes and dementia are numerous; they include vascular lesions, inflammation, oxidative stress, elevated glycolysis end products, insulin resistance, abnormal insulin receptor signaling, insulin degradation, and insulin's relationship with A β -deposits [33]. Many researches support the hypothesis that AD responds to pathogenesis based on neuronal energy alterations, which are caused by insufficiencies in the glucose function. Metabolic abnormalities are associated with brain insulin growth factor, which regulates energy production and insulin resistance [34].

Diabetes results in insulin signaling dysfunction, leading to decreased mTOR activity; this produces a failure of autophagy causing A β accumulation, inhibits re-entry of post-mitotic neurons in the cell cycle, stimulates pathways of abnormal growth, and generates translational control loss and impaired neurogenesis [35]. S6 kinase (**S6K**) is activated by mTOR to phosphorylate and degrade the insulin receptor substrate-1 (**IRS-1**) which ultimately leads to desensitization of insulin. mTOR signaling interacts with A β -peptides and tau in their aggregated forms. Additionally, it has been proposed that the peptide is an activator of the phosphoinositide 3 kinase/protein kinase B (**PI3K/Akt**) pathway and that it stimulates the mTOR cascade [36]. Another common mechanism involving diabetes, obesity and AD is inflammation. Elevated levels of proinflammatory cytokines such as TNF- α , IL-6 and IL-1 β has been reported in previous studies with AD patients; however, in patients with diabetes, elevated TNF- α triggers the activation of several stress-kinases that phosphorylate to IRS-1 (in inhibitory serine residues) and interrupt insulin signaling. C-Jun NH2-terminal kinase (**JNK**) and double-stranded RNA-activated protein kinase are the main stress kinases; they are important regulators common to inflammation and metabolism. Since insulin signaling contributes to the normal functioning of neurons, any alteration-mediated inflammation in the neurons results in defective neuronal function [35].

The Vascular Hypothesis

The principal characteristic of the vascular hypothesis is the reduction of cerebral blood flow. This hypothesis suggests that the neurodegenerative process is initiated by chronic cerebral hypo perfusion caused by aging, oxidative stress, and vascular conditions such as hypertension,

atherosclerosis, and hyper cholesterolemia [37]. Hypo perfusion and hypoxia are one aspect of the problem, but the breakdown of the blood-brain barrier also results in accumulation of neurotoxic serum proteins in the brain, inflammation, as well as vascular and synaptic dysfunction, leading to defects in A β and Tau metabolism and clearance, which in turn cause vascular problems [38]. BBB dysfunction mediates the indirect neurotoxic effects of chronic hypo perfusion by promoting oxidative stress, inflammation and impaired glucose transport across the blood-brain barrier, and their permeability [39]. On the other hand, the deterioration of energy-dependent ion pumps, such as the ATP-dependent sodium pump and the sodium/hydrogen ion exchange, can lead to changes in intracellular pH due to alterations in electrolyte transport through the BBB, resulting in neurovascular disintegration [40].

In AD, neuronal loss is accompanied by cerebral vessel wall thickening, recruitment of macrophages, and formation of A β deposits in the vicinity of the cerebral vasculature. Thus, macrophages begin to accumulate between amyloid deposits and vessel walls. The mechanisms behind neuronal loss are not yet understood, but impaired trans-vessel oxygen, BBB function, and glucose delivery, along with reduced removal of toxic metabolites may predispose to neuronal death [41].

COMMON CAUSES OF NEURODEGENERATIVE DISORDERS

Genetic Mutations

Changes in DNA have been associated with the development of neuro degeneration; such changes may be controlled by epigenetic factors and also by hereditary changes, representing the familial form or “sporadic” mutations (less than 5%). There are also “idiopathic” genetic mutations induced by other factors such as β -amyloid precursor protein, which causes Alzheimer’s disease, α -synuclein, which causes Parkinson’s disease, and the Hunting in gene, which causes Huntington’s disease. Genetic mutations may induce changes in mitochondrial pathways, protein degradation, free radical and oxidative stress control, and immune system functions. These genetic mutations affect cell function, allowing apoptosis and inducing neuro degeneration [27,42,43].

Protein misfolding

One of the central points in neurodegenerative diseases is protein misfolding, a process associated with genetic mutations or triggered by external factors that induces incorrect structural protein formation and function. It subsequently leads to their aggregation in oligomer form and in some cases as plates, stored intra cellularly (Parkinson’s disease and Huntington’s disease), extracellularly (Alzheimer’s disease), and in neuro fibrillary tangles (Alzheimer’s and amyotrophic lateral sclerosis). These misfolded proteins allow for a classification of proteopathies in some neurodegenerative diseases. The protein oligomers induce a second brain reaction including toxic molecule formation, as well as oxidative stress, which induce cell dysfunction [1,2].

Protein Degradation Pathways

Intracellular misfolded proteins maybe regulated by a degradation system called the poly-ubiquitination-proteasome system. The polyubiquitination-proteasome system will select misfolded protein and through the ubiquitin enzyme forms an ubiquitin polymer with the protein, by ubiquitin ligase enzyme. The ubiquitinated protein is transported to the proteasome and degraded into small fragments. There is another process referred to as autophagy, which involves the degradation of large misfolded proteins that can damage the cell; in this process, lysosomal enzymes are responsible for carrying out programmed cell death by starvation. However, when these degradation pathways (the polyubiquitination-proteasome system and autophagy) fail in the degradation of misfolded proteins, cell damage can be induced by the generation of toxic molecules and oxidative stress [1,2,27].

Generation of Oxidative Stress and Toxic Molecules

Oxidative stress, which induces the generation of toxic molecules such as reactive oxygen species, nitric oxide, and reactive nitrogen species, maybe generated by misfolded proteins, alteration in the homeostasis of metals and excessive antioxidant action. The concentration of reactive oxygen species is controlled by the action of mitochondrial enzymes, such as superoxide dismutase and glutathione peroxidase; however, when these enzymes fail, the generation of toxic molecules by oxidative stress induces different reactions such as cell membrane peroxidation damage in the mitochondrial respiratory chain and excitotoxicity. Excitotoxicity, a main consequence of oxidative stress, is due to the increase in cytosolic calcium, astrogliosis and microglial activation, mitochondrial dysfunction, and proteasome damage. The active molecular mechanisms associated to neuronal apoptosis, and elimination of internal imbalance, is generated by oxidative stress [2,27,44,45].

Mitochondrial Dysfunction

The mitochondrion is an organelle, responsible in particular for providing energy (**ATP**) to the cell, through the electron transport chain. However, reactive oxygen species induce oxidative stress by two pathways of damage: the electron transport chain and mtDNA. Those changes induce mitochondria dysfunctions and decreased ATP calcium homeostasis compromise, membrane lipid peroxidation, and mitochondrial permeability. This dysregulation induces the intrinsic mitochondrial apoptotic pathways through the separation of the anti-apoptotic protein Bax/Bcl-2 complex, allowing the Bax protein to carry out an interaction with a voltage-dependent channel for opening and permeability for the calcium transition, processes that induce mitochondrial fragmentation. Subsequently, cytochrome C is released from the mitochondria, and caspase 9 is activated; this in turn activates caspase 3. The activation of the caspases triggers programmed cell death. Another consequence related to mitochondrial dysfunction has been associated with the increase in free radicals and oxidative stress, which induces neuro degeneration [2,27,28,46].

Neuro-Inflammatory Processes

The action of the immune system in the central nervous system in neurodegenerative diseases is complex. The inflammatory process in the central nervous system includes the activation of microglia cells, astrocytes, T-cell infiltration, major histocompatibility complex class II expression, and cytokine release. The activation of the inflammatory process may be due to extracellular aggregation of misfolded proteins, cellular debris as a product of neurodegeneration, oxidative stress, and other external agents. The inflammatory process is beneficial in the early stages of neurodegenerative diseases, because through phagocytosis neurons are cleaned by means of toxicants, in addition to performing repair functions. However, chronic activation of the immune system leads to over expression of pro-inflammatory cytokines and factors such as TNF- α , which impair phagocytosis and affect cell survival and generate an oxidative environment, promoting neurodegeneration through the apoptosis pathway [2,27,47].

In summary, neurodegeneration as in AD is a multifactorial disease, which is why a general pathological mechanism and appropriate treatment have not been found, but various etiological hypotheses have been proposed in order to understand a little about “the world” comprised by this disease.

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